

# Exhibit 7

## Specific Causation Expert Report: David Downs

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sufficiently intense to have caused Mr. Downs kidney cancer and that the toxins existed in the water for a sufficient duration of time to have caused a substantial exposure.

The International Agency for Research on Cancer (IARC) classified TCE, Vinyl Chloride and Benzene as Group 1 carcinogens and PCE as probably carcinogenic to humans (Group 2A), linking exposure to increased risk of cancer.<sup>6,7</sup> The EPA concluded strong support for a relationship between TCE and kidney cancer.<sup>5</sup> The 2015 National Toxicology Program (NTP) monographs on TCE concluded strong support for the relationship between TCE exposure and kidney cancer.<sup>8</sup> The ATSDR reports from Camp Lejeune concur with the evaluations made by IARC, EPA and NTP.<sup>4</sup>

Just recently, the EPA publicly announced bans on TCE and PCE.<sup>9</sup> The EPA made clear, for both TCE and PCE, that among the reasons for the ban was the connection between TCE and PCE to kidney cancer at low levels.

## **VI. Mode of Exposure and Mechanism of Action between Camp Lejeune Chemicals and Kidney Cancer**

I have reviewed the general causation reports of Drs. Hatten and Bird and agree with their statements as to the mode of exposure and mechanism of actions for these chemicals as it pertains to kidney cancer.

Exposure to chlorinated compounds may be sustained through inhalation, ingestion, and dermal absorption.<sup>10</sup> Considering the compounds of interest in this study, epidemiologic, occupational, and environmental studies have identified dry-cleaning solvents, degreasing fluids, and contaminated groundwater as key sources of occupational and environmental exposure of the toxins in the water. Metabolites of these chlorinated compounds are also preferentially excreted and concentrated in the urine potentially heightening the relative exposure experienced by the GU tract.<sup>6</sup>

The literature demonstrates data regarding the mechanism of carcinogenesis with respect to TCE and PCE. Bacterial and animal studies have demonstrated the mutagenicity of each compound.<sup>6</sup>

Currently, the most is known about potential mechanisms of carcinogenesis with respect to TCE. DNA methylation and chromosomal aberration represent reasonable and medically valid etiologies for a genotoxic carcinogenic effect of TCE based on studies of human subjects.<sup>6</sup> One epigenome-wide association study of humans demonstrated that TCE exposure increased methylation variation globally in white blood cells ( $p=0.00375$ ), suggesting that TCE may contribute to epigenetic drift.<sup>11</sup>

When it comes to kidney cancer specifically, several mechanisms have been researched. Many studies have focused on mutation of the *VHL* gene (a common mutation in renal cell carcinoma). Brauch et al. identified 44 patients with RCC who had been exposed to TCE. 33 of 44 had VHL mutations and 14 of these had multiple.<sup>12</sup> Moreover, only patients with high and medium exposure to trichloroethylene, but not low exposure, had VHL mutations, and there was a significant correlation between severity of exposure and presence of multiple mutations.<sup>12</sup> A follow-up of the previous study compared the characteristics of VHL mutations in cases of renal

cell carcinoma in people exposed to trichloroethylene (n = 17) and cases in people not exposed to trichloroethylene (n = 21).<sup>13</sup> Samples of tissues from tumor and non-tumor areas of the kidney were collected from the 38 cases, micro dissected, and amplification and sequencing of the individual VHL exons was conducted using polymerase chain reaction (PCR).<sup>13</sup> Cases of renal cell carcinoma associated with occupational exposure to trichloroethylene were reported to be diagnosed at a younger age (median, 57.5 years) compared with cases with no exposure to trichloroethylene (median, 67 years).<sup>13</sup> In addition, mutation characteristics of the VHL gene differed according to trichloroethylene-exposure status, as exposed cases had a higher frequency of somatic mutations (82% in exposed versus 10% in unexposed), multiple mutations (50% in exposed versus 0% in unexposed), and frequency of the nucleotide 454 C→T hot spot mutation previously identified (38% in exposed versus 0% in unexposed).<sup>13</sup>

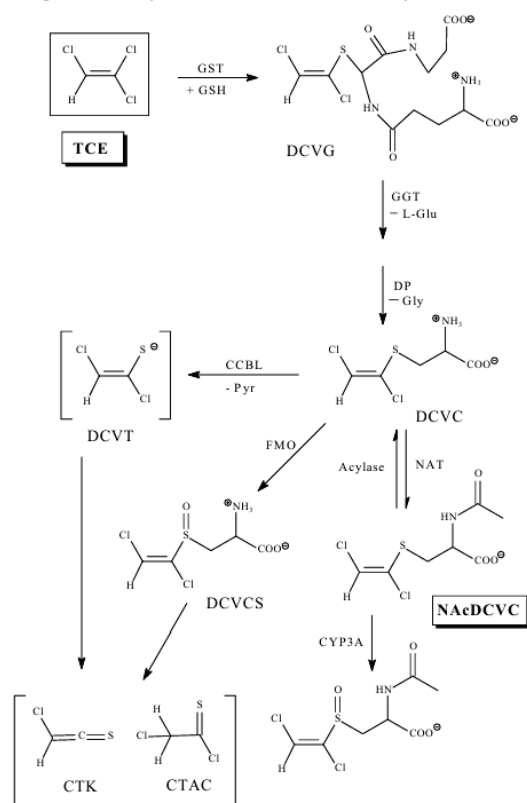
Additionally, it has been discussed in the literature as to whether TCE and PCE indirectly lead to mutagenesis through accumulation of a2u-globulin.<sup>6</sup> Accumulation of this compound in renal proximal tubules has been thought to lead to local renal changes resulting in increased cellular proliferation.<sup>6</sup> There is data to suggest PCE specifically may cause oxidative stress at the cellular level, which results in carcinogenesis directly.<sup>6</sup>

Further, studies indicate that several breakdown products have been thought to demonstrate mutagenic effects. Glutathione-dependent conjugation is a trichloroethylene - metabolism pathway that results in formation of several toxicologically relevant metabolites (1,2-dichlorovinyl) glutathione (DCVG) and S-(1,2-dichlorovinyl) L-cysteine (DCVC) that can accumulate in the renal proximal tubules based on a genetic polymorphism in the proximal renal tubular organic anion transporter (OAT) protein. DCVG exhibited direct acting mutagenicity, with kidney mitochondria, cytosol, or microsomes enhancing the effects and AOAA diminishing, but not abolishing, the effects.<sup>14</sup> Importantly, the addition of liver subcellular fractions did not enhance the mutagenicity of DCVG, consistent with metabolism in situ (via GGT and dipeptidase) playing a significant role in the genotoxicity of the resulting cysteine conjugates in the kidney.<sup>14</sup> In the same study, DCVC exhibited direct-acting mutagenicity, with kidney mitochondria or cytosol enhancing the effects and AOAA diminishing, but not abolishing, the effects.<sup>14</sup> Jaffe et al. (1985) further reported DNA strand breaks after administration of DCVC in vivo, in isolated perfused kidneys.<sup>15</sup> A study using porcine kidney tubular epithelial LLC-PK1 cells also reported increased expression of the proto-oncogene c-Fos in the DCVC-derived clones.<sup>16</sup> Overall, these studies support mutagenicity in the kidney of TCE-derived compounds. The following are charts that depict the likely carcinogenic effects of these chemicals:

\*Metabolites identified in blood, urine, or breath after *in vivo* PCE exposure (rodent or human).

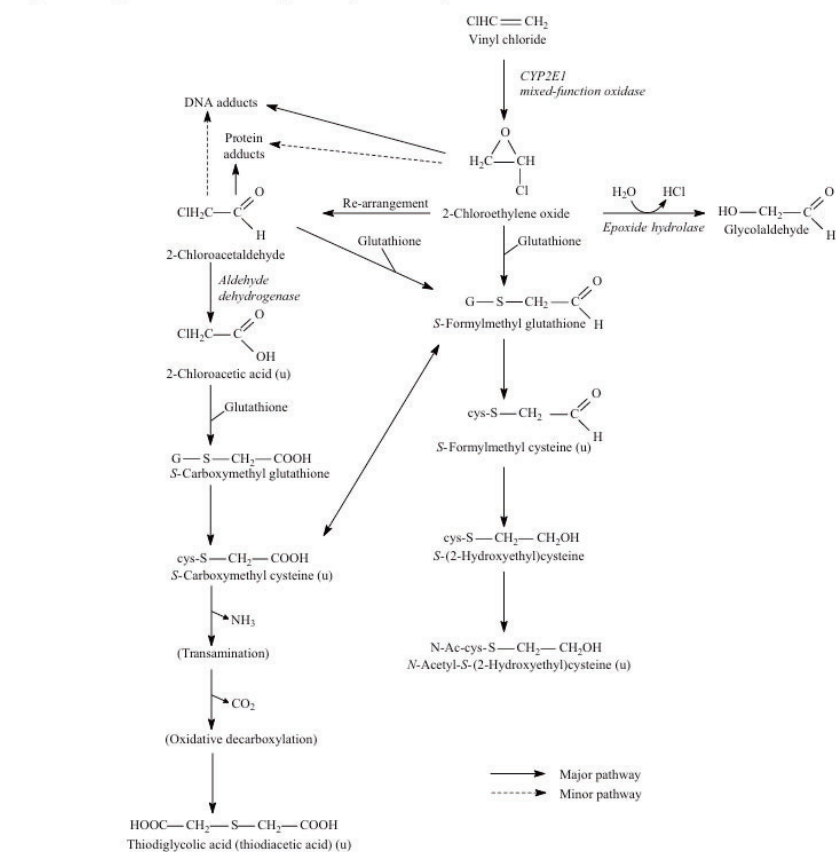


Fig. 4.2 Scheme for glutathione-dependent metabolism of trichloroethylene



Trichloroethylene (trichloroethylene) undergoes conjugation with glutathione (GSH) to yield the GSH S-conjugate DCVG. After processing to yield the cysteine S-conjugate DCVC, three potential fates are detoxication to yield the mercapturate NAcDCVC or bioactivation by either the cysteine conjugate β-lyase to yield dichlorovinylthiol, which rearranges to yield thioacylating species, or the flavin-containing monooxygenase to yield DCVC sulfoxide. The mercapturate can also be deacetylated to regenerate DCVC or it can undergo CYP3A-dependent sulfoxidation. Names of metabolites than are recovered in urine are shown in boxes and those that are chemical unstable or reactive are shown in brackets. Abbreviations: CCBL, cysteine conjugate β-lyase; CYP3A, cytochrome P-450 3A; CTAC, chlorothionoacetyl chloride; CTK, chlorothioketene; DCVC, S-(1,2-dichlorovinyl)-L-cysteine; DCVG, S-(1,2-dichlorovinyl)glutathione; DCVCS, DCVC sulfoxide; DCVT, 1,2-dichlorovinylthiol; DP, dipeptidase; FMO, flavin-containing monooxygenase; GGT, γ-glutamyltransferase; Gly, glycine; GSH, glutathione; GST, GSH S-transferase; L-Glu, L-glutamic acid; NAcDCVC, N-acetyl-S-(1,2-dichlorovinyl)-L-cysteine; NAcDCVCS, NAcDCVC sulfoxide; NAT, N-acetyltransferase.

(IARC 2014)

**Fig. 4.1 Proposed metabolic pathways for vinyl chloride**

From [Barbin et al. \(1975\)](#), [Plugge & Safe \(1977\)](#), [Green & Hathway \(1977\)](#), [Guengerich & Watanabe \(1979\)](#), [Guengerich et al. \(1979\)](#), [Bolt et al. \(1980\)](#), adapted from [ATSDR \(2006\)](#).  
CYP, cytochrome P450; (u), excreted in urine

(IARC 2012)

Vinyl chloride is a known carcinogen in humans according to the IARC, U.S. Department of Health and Human Services, and ATSDR.<sup>7,4,17</sup> “It is mutagenic, usually in the presence of metabolic activation, in various assays with bacteria, yeast or mammalian cells; it is also clastogenic *in vivo* and *in vitro*. Vinyl chloride induces unscheduled DNA synthesis, increases the frequency of sister chromatid exchange in rat and human cells, and increases the frequency of chromosomal aberrations and micronucleus formation in mice, rats, and hamsters *in vivo*.”<sup>7</sup>

## VII. Kidney Cancer is Caused by TCE, PCE and Vinyl Chloride According to the Epidemiology and Other Literature

I have reviewed the General Causation reports of Drs. Hatten and Bird who detailed a robust analysis of the epidemiology, toxicology and mechanism of action for the four main toxins at issue. These opinions and the data at issue in those reports support my opinions in this case.

### a. TCE and Kidney Cancer

TCE is known to cause kidney cancer.<sup>4,6,8,18,19,20,21,22</sup> There are several particularly informative studies in this space. Zhao et al., a cohort study of aerospace workers, performed a rigorous estimation of exposure using a job exposure matrix (JEM).<sup>18</sup> To assess exposure-response, exposures were divided into low, medium, and high-dose groupings.<sup>18</sup> High exposure

significantly correlated with developing kidney cancer (95% CI 4.9, 1.23–19.6).<sup>18</sup> Representing a strength of the study smoking was excluded as a potential confounder.<sup>18</sup> A study by Charbotel et al., looked at TCE and kidney cancer.<sup>19</sup> The OR found was 2.16 (95% CI, 1.02–4.60).<sup>19</sup> Tobacco smoking and BMI were accounted for in the study. There was a significant dose-response relationship ( $p=0.04$ ).<sup>19</sup> Moore et al, a case control study of occupational exposure in central and eastern Europe, similarly rigorously defined dose-exposure and found significantly higher risk of kidney cancer in those with above median exposure (95% CI 2.41, 1.05-5.56).<sup>20</sup> Each of these studies demonstrated sound study design and importantly demonstrated significant exposure-response relationships between exposure to TCE and kidney cancer.

I also reviewed several meta-analyses done with regard to TCE and kidney cancer. Scott et al. performed a systematic review on TCE and kidney cancer.<sup>21</sup> The reported summary relative risk (RRm) was 1.27 (95% CI 1.13-1.43) for overall TCE exposure and kidney cancer risk. The RRm for the highest exposure group was 1.58 (95% CI: 1.28-1.96).<sup>21</sup> Karami et al. is another meta-analysis that showed similar results and utilized mostly the same studies.<sup>22</sup> Subsequently, three additional studies published in 2013, Christensen et al., Hansen et al., and Vlaanderen et al., demonstrated no increase in kidney cancer among TCE-exposed individuals, but all are noted for having low incidence of high-exposure and/or less precise evaluation of dose-exposure, biasing results toward the null.<sup>23-25</sup> Accounting for some or all of these later studies, the 2014 International Agency for Research on Cancer (IARC) and the 2015 National Toxicology Program (NTP) monographs on TCE concluded strong support for a relationship between TCE exposure and kidney cancer.<sup>6,8</sup> The ATSDR reports from Camp Lejeune concur with the evaluations made by IARC, EPA and NTP.<sup>4</sup> Based on the overall consistent findings of increased risks of kidney cancer from exposures to TCE and the supporting mechanistic information, there is sufficient evidence for causation for TCE and kidney cancer. This will be used in this specific causation analysis.

## **b. PCE and Kidney Cancer**

Several studies demonstrate a statistically significant positive relationship between PCE exposure and incidence of kidney cancer.<sup>26,27,28,29,30,31</sup> The case control study by Karami et al. supplies the strongest epidemiologic data in support of kidney carcinogenesis for PCE.<sup>27</sup> The authors demonstrated a doubled risk of kidney cancer in dry-cleaning workers likely occupationally exposed to PCE.<sup>27</sup> This heightened relative risk was 2.0 (95% CI: 0.9-4.4).<sup>27</sup> Additionally, Mandel et al. conducted a wide-ranging study of various occupational exposures. Overall, 302/1732 cases with kidney cancer had been occupationally exposed to dry-cleaning solvents.<sup>28</sup> The study found a significant relationship between employment in dry cleaning/laundry and kidney cancer in all men OR 1.4 (95% CI 1.1-1.7) and all women OR 1.6 (95% CI 1.0-2.7).<sup>28</sup> There are several studies that deal with this topic that failed to demonstrate any significant relationship between PCE exposure and kidney cancer.<sup>32</sup> However, this does not negate the significant body of literature with positive findings of a causal relationship between PCE and kidney cancer. There are other kidney cancer studies and literature cited by general causation experts Drs. Hatten and Bird that support this proposition as well.

In a context similar to that of Camp Lejeune, Aschengrau et al. studied a population exposed to PCE-contaminated drinking water on Cape Cod, MA.<sup>29</sup> The study results showed that any PCE exposure (OR 1.23) and low PCE exposure (OR 1.36) demonstrated elevated measures of association with kidney cancer in an analysis not accounting for latency.<sup>29</sup>

Some animal studies suggest a relationship between exposure to PCE and kidney cancer. Male mice were fed varying levels of PCE-laced corn oil ranging from dosages of 450-1100mg/kg over a 78 week period.<sup>30</sup> Exposure to tetrachloroethylene caused toxic nephropathy (characterized in this study as degenerative changes in the proximal convoluted tubules at the junction of the cortex and medulla, with cloudy swelling, fatty degeneration, and necrosis of the tubular epithelium). One mouse developed renal cell carcinoma.<sup>30</sup> A similar study of inhalation of PCE exposed rats to air containing tetrachloroethylene (purity, 99.9%) at concentrations of 0, 200, or 400 ppm (0, 1360, or 2720 mg/m<sup>3</sup>) for 6 hours per day on 5 days per week for up to 103 weeks.<sup>31</sup> An increase in uncommonly occurring adenoma or carcinoma (combined) of the kidney tubule was observed in male rats (1/49, 3/49, 4/50); the historical incidence of these neoplasms in control male rats in inhalation studies conducted by the National Toxicology Program (NTP) at that time was 4 out of 1968 (0.2 ± 0.6%).<sup>31</sup>

### c. Vinyl Chloride and Kidney Cancer

IARC has stated “There is *sufficient evidence* in humans for the carcinogenicity of vinyl chloride. Vinyl chloride causes angiosarcoma of the liver, and hepatocellular carcinoma. There is sufficient evidence in experimental animals for the carcinogenicity of vinyl chloride.”<sup>7</sup>

The EPA has classified vinyl chloride as “Group A, “human carcinogen.”<sup>33</sup> The NTP has also found that vinyl chloride “is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans.”<sup>34</sup>

Hu 2002 studied kidney cancer with exposure to vinyl chloride. They reported an elevated risk with an OR of 2.0 (95% CI 1.2–3.3).<sup>35</sup> There was a monotonic response found for Vinyl Chloride and kidney cancer.

The many studies looking particularly at Camp Lejeune show a causal relationship between vinyl chloride and kidney cancer.

## VIII. The Levels of The Chemicals at Camp Lejeune Are Known to Cause Kidney Cancer

Current U.S. maximum contamination levels in drinking water are 5 µg/L for TCE, PCE and benzene, and 2 µg/L for vinyl chloride. Levels of TCE, PCE, and VC were significantly higher than those deemed acceptable by government agencies. As discussed by Bove et al, exposure through drinking water represented a significant exposure, but inhalation exposure through solubilized chemicals in water vapor sustained during showering and bathing also accounts for additional exposure.<sup>1,2</sup>

As outlined above, increased exposure to TCE demonstrates strong evidence for causing kidney cancer. This is supported by reviews from credible government agencies. PCE’s contribution to